



Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Recommendations for Use of Antiretroviral Drugs during Pregnancy: Overview (Last updated December 12, 2019; last reviewed December 12, 2019)

Panel's Recommendations

- When choosing an antiretroviral (ARV) drug regimen for a pregnant woman, providers and patients should consider multiple factors, including adverse effects, drug interactions, pharmacokinetics (PKs), convenience of the individual drugs and drug combinations in the regimen, available pregnancy safety and outcome data, and the patient's resistance test results and comorbidities (AIII).
- The same regimens that are recommended for the treatment of nonpregnant adults should be used in pregnant women when sufficient data suggest that appropriate drug exposure is achieved during pregnancy; clinicians should weigh the risks of adverse effects for women, fetuses, or infants against the benefits of these regimens and recognize that there are often incomplete data on the safety of ARV drugs in pregnancy (AII). For more information, see Tables 4 and 5.
- In most cases, women who present for obstetric care on fully suppressive ARV regimens should continue their current regimens (AIII).
- PK changes in pregnancy may lead to lower plasma levels of drugs and necessitate increased doses, more frequent dosing, boosting, or more frequent viral load monitoring (AII).

Updated Panel Recommendations Regarding the Use of Dolutegravir in Pregnancy:

- Dolutegravir (DTG) exposure around the time of conception has been associated with a small but significant increase in the risk of infant neural tube defects (NTDs) in Botswana (0.3%). This risk was higher than the risk for NTDs in infants born to women who were receiving efavirenz (0.05%) and women without HIV (0.08%). There are not enough data to determine the risk of NTDs with preconception use of all Preferred and Alternative regimens, including DTG, in the United States. Based on the available evidence, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends DTG as a **Preferred drug for pregnant women, irrespective of trimester (AII)**, and an **Alternative drug for women who are trying to conceive (AIII)**.
- The Panel emphasizes the importance of counseling and informed decision-making regarding all ARV regimens for people with HIV (AIII). For additional information, see [Preconception Counseling and Care for Women of Childbearing Age Living with HIV](#), [Teratogenicity](#), [Appendix D: Dolutegravir Counseling Guide for Health Care Providers](#), and Tables 4 and 5.
- When DTG use is continued after delivery, clinicians should discuss reproductive desires, the risks and benefits of conceiving on DTG, and contraceptive options (AIII). See [Preconception Counseling and Care](#) and [Postpartum Care](#) for more information.
- Folic acid is known to prevent NTDs in the general population. All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily (AI). There is no established link between the use of DTG and impaired folate metabolism, nor is there evidence that folate supplementation prevents DTG-associated NTDs.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

This section provides an overview of the key clinical and pharmacokinetic (PK) issues that are relevant to the selection of specific antiretroviral (ARV) drugs for use in pregnancy. Additional [recommendations for women who have never received antiretroviral therapy \(ART-naïve women\)](#), [women who are currently receiving ART](#), and [women who were previously on ART or who have used ARV drugs for prophylaxis](#) are listed in the three sections that follow this overview. [Table 4](#) provides specific information about recommended ARV drugs when **initiating** ART in treatment-naïve pregnant women. The table also includes considerations for ARV regimen selection and modification in pregnant women who are treatment-experienced and women who are attempting to become pregnant.

[Table 5](#) consolidates situation-specific recommendations about the use of ARV drugs in women with HIV during conception and pregnancy into a single table for ease of reference. [Table 5](#) includes recommendations for the use of ARV drugs in the following situations:

- Initiating ART in pregnant women who have never received ARV drugs;
- Continuing ART in women who become pregnant while on a fully suppressive regimen that has been well tolerated;

- Restarting ART in pregnant women who received ART or ARV drugs for prophylaxis in the past;
- Changing to a new ARV regimen in pregnant women whose current ART is not well tolerated and/or is not resulting in virologic suppression; *and*
- Initiating or modifying ART in women who are trying to conceive.

[Table 8](#) and [Appendix B](#) provide information about individual drugs, including dosing and PK data in pregnancy.

Drugs of known benefit to women should not be withheld during pregnancy unless there are known adverse effects to the woman, fetus, or infant, and these adverse effects outweigh the benefits to the woman or adequate drug levels are not likely to be attained during pregnancy. Pregnancy and potential for pregnancy **should not preclude** the use of optimal drug regimens. **The decision about which ARV drugs to use during pregnancy should be made by a woman after discussing the known and potential benefits and risks to her and her fetus.**¹

The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration review that are related to the treatment of adult women with HIV, both those who are pregnant and those who are not. The durability, tolerability, and simplicity of a medication regimen are particularly important for ensuring adherence and preserving future treatment options. Regimen selection should be based on several factors that apply to all pregnant women, as well as factors that will vary for individual patients.

Pregnancy-related factors include:

- Potential teratogenic effects and other short-term and long-term adverse effects on fetuses or newborns, including preterm birth, mutagenicity, and carcinogenicity;
- **Available safety and outcome data on the** use of the drug in pregnancy;
- PK changes in pregnancy; *and*
- Potential adverse effects for the woman, especially those that may be exacerbated during pregnancy.

Individual-level factors include:

- Potential drug interactions with other medications;
- Results of genotypic resistance testing and the woman's prior exposure to ARV drugs;
- Comorbidities;
- Ability of the patient to adhere to a regimen; *and*
- Convenience.

The Panel uses information from several sources to develop recommendations on specific drugs or regimens for pregnant women. These sources include:

- Data from randomized clinical trials and prospective cohort studies that demonstrate durable viral suppression in pregnancy, as well as immunologic and clinical improvement;
- Incidence rates and descriptions of short-term and long-term drug toxicity of ARV regimens;
- Evidence from clinical studies of risk of maternal toxicity, teratogenicity, adverse pregnancy outcomes, and adverse infant outcomes;
- Specific knowledge about drug tolerability and simplified dosing regimens;
- Known efficacy of ARV drug regimens in reducing perinatal transmission of HIV;
- PK (drug exposure) data during pregnancy;

- Data from animal teratogenicity studies; *and*
- Antiretroviral Pregnancy Registry data and other post-marketing surveillance data.²

Categories of ARV drugs and drug combinations for use in pregnancy include:

- **Preferred:** Drugs or drug combinations are designated as *Preferred* for therapy in pregnant women when clinical trial data in adults have demonstrated efficacy and durability with acceptable toxicity and ease of use, and pregnancy-specific PK data are available to guide dosing. In addition, the **available data must suggest a favorable risk-benefit balance for the drug or drug combination compared to other ARV drug options; the assessment of risks and benefits should incorporate outcomes for women, fetuses, and infants. Some Preferred drugs or regimens may have minimal toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or who are trying to conceive.**
- **Alternative:** Drugs or drug combinations are designated as *Alternative* options for therapy in pregnant women when clinical trial data in adults show efficacy and the data in pregnant individuals are generally favorable but limited. Most *Alternative* drugs or regimens are associated with more PK, dosing, tolerability, formulation, administration, or interaction concerns than those in the *Preferred* category, but they are acceptable for use in pregnancy. **Some Alternative drugs or regimens may have known toxicity or teratogenicity risks that are offset by other advantages for women with HIV who are pregnant or who are trying to conceive.**
- **Insufficient Data to Recommend:** The drugs and drug combinations in this category are approved for use in adults, but pregnancy-specific PK or safety data are too limited to make a recommendation for use in pregnant women. In some cases, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on ART that has been well tolerated.
- **Not Recommended Except in Special Circumstances:** Although some drugs are not recommended for initial ART in ART-naïve women due to specific safety concerns or very limited safety and efficacy data in pregnancy, there may be circumstances in which ART-experienced women need to initiate or continue using specific drugs to reach or maintain viral suppression.
- **Not Recommended:** Drugs and drug combinations listed in this category are not recommended for use in pregnancy due to inferior virologic efficacy or potentially serious maternal or fetal safety concerns. They may also be categorized as not recommended for initial therapy in ARV-naïve populations regardless of pregnancy status. This category includes drugs or drug combinations for which PK data demonstrate low drug levels and risk of viral rebound during pregnancy. Levels of these drugs are often low in late pregnancy (during the second and third trimesters), when risk for perinatal transmission is high if maternal viremia occurs. In some situations, it may be appropriate to continue using these drugs or drug combinations in women who become pregnant on fully suppressive ART that has been well tolerated, though viral load monitoring should be performed more frequently in these instances. See [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy](#) and [Monitoring of the Woman and Fetus During Pregnancy](#).

Selection of ARV drugs **should be individualized** according to a pregnant woman's specific ARV history, the results of drug-resistance assays, and the presence of comorbidities, **as well as the individual women's preferences for balancing known and unknown risks and benefits.** In pregnant women (as in nonpregnant adults, adolescents, and children), ART that includes at least three agents is recommended. For ARV-naïve women, an ARV regimen that includes two nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir (RTV)-boosted protease inhibitor (PI) or an integrase strand transfer inhibitor (INSTI) is preferred (Table 4). In general, **women who are already on a fully suppressive regimen when pregnancy occurs should continue their regimens.** Key exceptions include regimens that involve medications with a high risk

for toxicity or inferior virologic efficacy that are not recommended for use in adults (e.g., didanosine [ddI], indinavir [IDV], nelfinavir [NFV], stavudine [d4T], and treatment-dose RTV) and drugs that should not be used in pregnant women because of PK or toxicity concerns (see [Table 4](#)).

For women who have achieved virologic suppression and who are receiving regimens that may increase the risk of virologic failure during pregnancy (e.g., darunavir/cobicistat [DRV/c], atazanavir/cobicistat [ATV/c], and elvitegravir/cobicistat [EVG/c]), consider changing the ARV regimen or continuing the same regimen and increasing the frequency of viral load monitoring. Women who are not fully suppressed and who are currently taking ART should be carefully evaluated for adherence and genotypic resistance, with every effort made to achieve full virologic suppression rapidly through adherence interventions or medication changes (see [Lack of Viral Suppression](#)). When treating women who have previously received ARV drugs but who are not currently taking ARV drugs, clinicians will need to take previous regimens and the potential for genotypic resistance into consideration. Specific recommendations for each type of patient are described in [Table 5](#) and in the following sections: [Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs](#), [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy](#), and [Pregnant Women Living with HIV Who Have Previously Received Antiretroviral Treatment or Prophylaxis but Are Not Currently Receiving Any Antiretroviral Medications](#).

Pharmacokinetic Considerations for Antiretroviral Drugs

Physiologic changes that occur during pregnancy can affect drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially increasing the risk for virologic failure or drug toxicity.³⁻⁵ During pregnancy, gastrointestinal transit time becomes prolonged; body water and fat increase throughout gestation, and these changes are accompanied by increases in cardiac output, ventilation, and liver and renal blood flow; plasma protein concentrations decrease; renal sodium reabsorption increases; and changes occur in cellular transporters and drug metabolizing enzymes in the liver and intestine. Placental transport of drugs, compartmentalization of drugs in the embryo/fetus and placenta, biotransformation of drugs by the fetus and placenta, and elimination of drugs by the fetus also can affect drug PKs in the pregnant woman. In general, the PKs of NRTIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are similar in pregnant and nonpregnant women (although PK data for etravirine [ETR] are limited). PI and INSTI PKs are more variable, particularly during the second and third trimesters. Currently available data on the PKs and dosing of ARV drugs in pregnancy are listed for each drug below and summarized in [Table 8](#).

Nucleoside Reverse Transcriptase Inhibitors

Preferred NRTI combinations for use in ARV-naïve pregnant women are: abacavir (ABC) used in combination with lamivudine (3TC), and tenofovir disoproxil fumarate (TDF) used in combination with emtricitabine (FTC) or 3TC.

Abacavir plus lamivudine is the NRTI component in some *Preferred* regimens for nonpregnant adults. It offers the advantage of once-daily dosing and is well tolerated in pregnancy.⁶ Testing for the HLA-B*5701 allele should be performed and documented as negative before starting ABC, and women should be educated about symptoms of hypersensitivity reactions. Clinicians should determine whether a patient has hepatitis B virus (HBV)/HIV coinfection; for women with HBV/HIV coinfection, two NRTIs that are active against HBV should be chosen (e.g., TDF with FTC or 3TC) in place of ABC plus 3TC (see [HBV/HIV Coinfection](#)).

TDF plus emtricitabine or lamivudine is the NRTI component in some *Preferred* regimens for nonpregnant adults. This combination has several advantages, including extensive experience with use in pregnancy, once-daily dosing, enhanced activity against HBV, and less toxicity than zidovudine (ZDV) plus 3TC. Although there have been concerns about bone and growth abnormalities in infants who were exposed to TDF *in utero*, the duration and clinical significance of study findings require further evaluation (see [Tenofovir Disoproxil Fumarate](#)).⁷ Although some authors have suggested that ZDV plus 3TC should be used in place of TDF plus FTC,⁸ this suggestion is based on data from a single study, the Promoting Maternal

and Infant Survival Everywhere (PROMISE) trial.⁹ The generalizability of the PROMISE findings is limited by important study design and statistical considerations (for details, see [Tenofovir Disoproxil Fumarate](#) and [Lopinavir/Ritonavir](#)). After considering all available evidence, the Panel concluded that the assessment of expected benefits and risks favored the use of TDF plus FTC over ZDV plus 3TC. The Panel maintains the *Preferred* classification for TDF plus FTC and the *Alternative* classification for ZDV plus 3TC.

Zidovudine plus lamivudine is an *Alternative* NRTI combination for ARV-naïve pregnant women. Despite proven efficacy in preventing perinatal HIV transmission and extensive experience with use in pregnancy, this NRTI combination is classified as *Alternative* rather than *Preferred* because it requires twice-daily dosing and is associated with higher rates of mild-to-moderate adverse effects, including nausea, headache, and reversible maternal and neonatal anemia and neutropenia (see [Zidovudine](#)).

Pregnant women who are receiving **didanosine** or **stavudine** should be switched to *Preferred* or *Alternative* medications.

Safety and PK data for the use of **tenofovir alafenamide** (TAF) during pregnancy are insufficient to recommend initiating this medication in pregnant women. However, it may be appropriate to continue using TAF in some pregnant women who are virally suppressed. Available PK data for TAF indicate that exposure is adequate in pregnancy, and a change in dosing is not indicated.^{10,11}

Integrase Strand Transfer Inhibitors

Updated Guidance about the Use of Dolutegravir in Pregnancy: **Dolutegravir** (DTG) is now a *Preferred* INSTI for pregnant women because there are sufficient data about the efficacy and safety of DTG when it is initiated during pregnancy. The Panel has reviewed all the data available as of August 2019 regarding DTG use preconception or during the first trimester of pregnancy. Based on these data, DTG **is considered a Preferred drug for use throughout pregnancy** and an **Alternative drug for women who are trying to conceive**; these designations reflect concerns about a possible increased risk of neural tube defects (NTDs). The decision to designate DTG as a *Preferred* ARV drug for therapy in pregnant women, irrespective of trimester, was based on several factors. First, DTG is associated with higher rates of virologic suppression, faster rates of viral load decline, and a higher genetic barrier to drug resistance than other *Preferred* and *Alternative* agents. Second, a recent study that evaluated a large number of pregnancies has shown that the risk of NTDs is lower than previously reported in preliminary data. This risk is also largely limited to a short period of time (before 6 weeks post-last menstrual period). A very small minority of women with HIV initiate their first ARV regimen during this period of time. Some Panel members would avoid using DTG in women who are initiating ART before 6 weeks gestation. After this time, any additional risk of NTDs due to DTG is minimal. Third, data are extremely limited on the risks that are associated with using other *Preferred* and *Alternative* ARV drugs preconception or in very early pregnancy; this lack of data does not indicate either the presence or absence of risk when using alternatives to DTG.

While this recommendation reflects Panel consensus, some Panel members favored recommending the use of DTG in the first trimester as an *Alternative* ARV drug, and the Panel discussed several possible recommendation ratings for the use of DTG in women who are trying to conceive, which ranged from not recommended to *Preferred*. The variety of proposed recommendations reflects how individual Panel members incorporate the available data into clinical decisions. Panel members weighed not only the updated data about DTG-associated NTD risk in specific settings (primarily Botswana), but also the important lack of comparable data about NTD risk with the use of DTG in other settings and about the risk of NTDs when using other *Preferred* and *Alternative* ARV drugs and drug combinations. All of these individual clinical decisions were made after reviewing the same available data, underscoring the importance of **counseling all patients on the risks and benefits of ARV drugs in order to promote informed, individual decision-making** (see [Appendix D: Dolutegravir Counseling Guide for Healthcare Providers](#)).¹²

It is important to weigh the available data about risks with DTG against what is known (or not known) about risks of NTDs with other *Preferred* and *Alternative* agents. These agents include atazanavir/ritonavir

(ATV/r), darunavir/ritonavir (DRV/r), and raltegravir (RAL) (Preferred), and lopinavir/ritonavir (LPV/r), efavirenz (EFV), rilpivirine (*Alternative*). Of these, systematic birth surveillance data are available only for EFV. Other adverse pregnancy outcomes are more common than NTDs and should also be considered. The use of PIs has been associated with an increased risk of preterm birth, which may lead to increases in infant morbidity and mortality. In the Botswana study, the risks of adverse pregnancy outcomes other than NTDs were similar for women who received DTG-based regimens and women who received EFV-based regimens.¹³ However, tolerability and long-term viral suppression may be enhanced with DTG-based regimens (see [Combination Antiretroviral Regimens](#) and [Maternal and Neonatal Outcomes](#)).^{13,14}

For additional information and recommendations about the use of DTG before conception and during pregnancy, see [Preconception Counseling and Care for Women of Childbearing Age Living with HIV](#), [Teratogenicity](#), [Pregnant Women Living with HIV Who Have Never Received Antiretroviral Drugs](#), and [Pregnant Women Living with HIV Who are Currently Receiving Antiretroviral Therapy](#).

Data on use of Dolutegravir before Conception and During Pregnancy: In May of 2018, an unplanned interim evaluation of the Botswana birth surveillance data revealed four NTDs among infants born to 426 women (0.94%) who conceived while taking DTG-based ART.¹³ These data were updated during a planned analysis that included data through March of 2019. Five NTDs occurred among 1,683 infants born to women who received preconception DTG (0.30%; 95% confidence interval [CI], 0.13% to 0.69%). The risk of NTDs was higher among women who received DTG than the risks observed for women who received any ARV regimen that did not include DTG (0.10%; 95% CI, 0.06% to 0.17%), women who received EFV-based ART (0.04%; 95% CI, 0.01% to 0.11%), women who initiated DTG during pregnancy (0.03%; 95% CI, 0.00% to 0.15%), and women without HIV (0.08%; 95% CI, 0.06% to 0.10%).¹⁵ Several other surveillance studies also contributed data in July 2019. The Botswana Ministry of Health used a comparable methodology to the Tsepamo study, including standardized outcome assessments for all available pregnancies, internal comparator groups, and ascertainment of outcomes among stillborn infants and for terminations. The Botswana Ministry of Health reported one NTD among 152 exposures at conception (0.66%; 95% CI, 0.02% to 3.69%).¹⁶ The Brazil Ministry of Health used a slightly different methodology, collecting data on the number of stillbirths and terminations, but excluding assessment of birth defects among these outcomes. The Brazil Ministry of Health reported no NTDs among infants born to 382 women who were receiving DTG at the time of conception (0.0%; 95% CI, 0.0% to 0.3%).

The Tsepamo study in Botswana also reported outcomes among women who started DTG-based or EFV-based ART **during pregnancy**, and reported that no birth defects occurred among infants born to 280 women who initiated DTG during the first trimester (all women initiated at >4 weeks gestational age and most initiated at >6 weeks gestational age) and no birth defects occurred among infants born to 729 women who initiated DTG in the second or third trimesters.¹³ These data were updated through March 2019. **Seventeen major external structural malformations were observed among 3,840 women who initiated DTG at any time during pregnancy (0.44%; 95% CI, 0.28% to 0.71%).**¹⁵ A multicenter retrospective cohort study of infants born to 66 women in the United States (42% of whom initiated DTG-based ART preconception, 24% of whom initiated DTG-based ART during pregnancy, and 33% of whom switched to DTG-based ART during pregnancy) found two anomalies and no NTDs.¹⁷ Published data that were reported to the Antiretroviral Pregnancy Registry through January 2019 include reports of anomalies in 11 of 307 infants (3.6%) who experienced first-trimester exposures to DTG and in six of 184 infants (3.3%) who experienced second-trimester or third-trimester exposures.²

Available data have not documented an increased risk of NTDs in infants born to women who received other INSTIs, but data are too limited to identify or calculate the specific risks that are associated with use of these drugs at the time of conception or during early pregnancy (see [Teratogenicity](#), [Dolutegravir](#), [Elvitegravir](#), [Raltegravir](#) and [Bictegravir](#)). To determine whether a drug carries an increased risk of a rare event such as an NTD, more than 2,000 periconception exposures need to be monitored to rule out a three-fold increase in risk. Clinicians are encouraged to submit data for all patients who conceive while receiving ARV drugs or who receive ARV drugs during pregnancy to the [Antiretroviral Pregnancy Registry](#).

If a causal association exists between the use of DTG and the occurrence of NTDs, it remains unknown what the mechanism of effect may be, whether folic acid deficiency is a mediating factor (and thus whether risk would be reduced by folic acid supplementation), and whether a similar risk may exist for other INSTIs. Although there is no established link between DTG use and impaired folate metabolism, nor is there evidence that folate prevents DTG-associated NTDs, folic acid is known to prevent NTDs in the general population.^{18,19} All pregnant women and women who might conceive should take at least 400 mcg of folic acid daily.

A randomized clinical trial that compared DTG plus two NRTIs to EFV plus two NRTIs in ART-naïve women who initiated therapy at a median gestational age of 31 weeks found that DTG-based ART produced more rapid viral suppression, with a greater proportion of women reaching an undetectable viral load (<50 copies/mL) at the time of delivery.²⁰ Although PK studies have found that DTG levels during the third trimester are lower than a pre-specified target level²¹ and lower than levels assessed postpartum,²² data regarding placental transfer and comparisons to levels in nonpregnant adults indicate that dose adjustments are not needed during pregnancy (see [Dolutegravir](#)).

Raltegravir (RAL) is a *Preferred* INSTI for use in ARV-naïve pregnant women, based on PK, safety, and other data on the use of RAL during pregnancy.²³⁻²⁹ Clinical trial data from both pregnant women and nonpregnant adults, as well as case series from pregnant women, suggest a more rapid viral decay with the use of RAL than with EFV or LPV/r.^{23,25,30-38} In an open-label, randomized clinical trial of late-presenting, ART-naïve pregnant women, the median time to achieve a viral load of <200 copies/mL was 8 days for women who received RAL-based ART and 15 days for women who received EFV-based ART. The decline in viral load was greater at 2, 4, and 6 weeks after initiating therapy in the women who received RAL than in those who received EFV.³⁹ A case study reported a marked elevation of liver transaminases after RAL was initiated in late pregnancy. This elevation resolved rapidly after stopping the drug, suggesting that monitoring of transaminases may be indicated when RAL is initiated in late pregnancy.⁴⁰

Although a once-daily formulation of RAL is approved for use in nonpregnant adults, there are insufficient PK data to support its use in pregnancy; twice-daily dosing remains the recommended dosing schedule.⁴¹

There are currently limited data on the use of **elvitegravir/cobicistat** in pregnancy.^{34,42} Data from the P1026 study suggest that coadministration of EVG and cobicistat (COBI) led to significantly lower levels of both drugs in the third trimester than in the postpartum period (levels in the third trimester were below the levels that are expected to lead to virologic suppression). Viral breakthroughs did occur, with only 74% of women maintaining viral suppression at delivery.^{43,44} Based on these data, EVG/c **is not recommended** for **initial** use in pregnancy. In a retrospective cohort of 134 women at nine tertiary care centers in the United States who received EVG at any time during pregnancy, viral suppression at delivery was 81% (88% among those who initiated EVG before pregnancy), and overall perinatal HIV transmission was 0.8%.⁴⁵ Providers should consider switching women who become pregnant while receiving EVG/c to more effective, recommended regimens. If an EVG/c regimen is continued, viral load should be monitored frequently. Some providers may monitor every 1 to 2 months in the second and third trimesters (see [Monitoring of the Woman and Fetus During Pregnancy](#) and [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment](#)).

Bictegravir (BIC) is an INSTI that is recommended for initial use in nonpregnant adults. There are no published data on BIC PKs, and extremely limited data on clinical outcomes in pregnancy; in an abstract presented by the manufacturer of BIC, no NTDs were reported among 18 women with prospectively reported periconception exposures.⁴⁶

Protease Inhibitors

Atazanavir/ritonavir and **darunavir/ritonavir** are *Preferred* PIs for use in ARV-naïve pregnant women, based on efficacy studies in adults and experience with use in pregnancy. Factors that impact the decision of which medication to use may include limitations in administering concomitant antacid, H2 blocker, or

proton pump inhibitors (ATV) and the requirement for twice-daily dosing (DRV). Although the use of once-daily dosing of DRV/r is approved for nonpregnant adults, there are insufficient PK data to support its use in pregnancy.⁴⁷ The *Alternative* PI is **lopinavir/ritonavir**. There is extensive clinical experience and PK data for the use of this combination in pregnancy, but it requires twice-daily dosing in pregnancy and frequently causes nausea and diarrhea; **it has also been associated with an increased risk of preterm delivery** (see [Combination Antiretroviral Drug Regimens](#) and [Maternal and Neonatal Outcomes](#)).

Atazanavir is associated with increased indirect bilirubin levels, which theoretically may increase the risk of hyperbilirubinemia in neonates; however, pathologic elevations have not been seen in studies to date.⁴⁸ In analyses from the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicity (SMARTT) study, *in utero* exposure to atazanavir was associated with statistically significant but small reductions in language and social-emotional scores compared to other drugs.⁴⁹ ATV exposure was also associated with risk of late language emergence at 12 months that was no longer significant at 24 months.^{50,51} The clinical significance of these findings associated with *in utero* ATV exposure is not known.

Darunavir/cobicistat and **atazanavir/cobicistat** **are not recommended** for use in pregnancy.^{44,52,53} PK studies suggest that low levels of both DRV and COBI occur in late pregnancy, and high rates of virologic failure have been observed in late pregnancy among women who were virally suppressed in early pregnancy. **Levels of ATV were similarly lower in the second and third trimesters;**⁴⁴ it is anticipated that the **virologic and transmission outcomes** with ATV/c will be similar to those observed with DRV/c and EVG/c. In addition, once-daily dosing of DRV **is not recommended** in pregnancy. For women who become pregnant on DRV/c or ATV/c, providers should consider switching to more effective, recommended regimens. If a regimen that contains DRV/c or ATV/c is continued for a woman who is virally suppressed, viral load should be monitored frequently (some providers may monitor monthly during the second and third trimesters; see [Monitoring of the Woman and Fetus During Pregnancy](#) and [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Treatment](#)).

Current data suggest that with standard adult dosing, plasma concentrations of LPV, ATV, and DRV are reduced during the second and/or third trimesters. Dose adjustment is recommended for LPV/r and may be considered for ATV/r, but dose adjustment is not recommended for DRV/r (see [Table 8](#)).⁵⁴ Specific dosing recommendations depend on the PI, an individual patient's treatment experience, and use (if any) of concomitant medications with potential for drug interactions.⁵⁴⁻⁶² Clinicians may consider therapeutic drug monitoring in specific situations.

Some older PIs—IDV, NFV, RTV (as the sole PI), and unboosted saquinavir or tipranavir—**are not recommended** for use in adults, and others—boosted or unboosted fosamprenavir, saquinavir/ritonavir and tipranavir/ritonavir—**are not recommended** for initial therapy in adults. These drugs **are not recommended** and should not be used in pregnant women due to concerns that include lower efficacy, toxicities, PK changes in pregnancy, and limited data and experience with use in pregnant women. See [Table 4](#), as well as [What Not to Use](#) and [Table 10](#) in the [Adult and Adolescent Antiretroviral Guidelines](#), for details on individual ARV drugs, ARV drug combinations, and ARV regimens that are not recommended or should not be used in adults.

Non-Nucleoside Reverse Transcriptase Inhibitors

There are no *Preferred* NNRTIs for use in ARV-naïve pregnant women.

Efavirenz is an *Alternative* NNRTI for both pregnant and nonpregnant ARV-naïve adults. **EFV may be suitable for women who desire a once-daily, fixed-dose combination regimen and who tolerate EFV without adverse effects.** Although data on the use of EFV in pregnancy are reassuring with regard to NTDs, and EFV is increasingly used during pregnancy worldwide, adverse effects associated with EFV include dizziness, fatigue, vivid dreams and/or nightmares, and increased risk of suicidality.^{13,63-67}

Although the EFV package insert cautions women not to become pregnant while taking EFV, recent large meta-analyses and the data from Botswana described above have been reassuring that the risk of NTDs in

infants with first-trimester EFV exposure is not greater than the risk in the general population.^{13,63-65,68} As a result, the Perinatal Guidelines do not restrict the use of EFV in pregnancy or in women who are planning to become pregnant; this is consistent with the British HIV Association Guidelines and the World Health Organization guidelines, both of which note that EFV can be used throughout pregnancy⁶⁹ (see [Teratogenicity and Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy](#)). A recent observational study reported a two-fold increased risk of microcephaly among infants born to 141 women receiving EFV compared to women receiving other ARV drugs in the United States, although factors such as alcohol use, unintended pregnancy, gestational age at ART initiation, changes in ARV practice patterns over time, and small numbers of women taking more recently recommended ARV drugs as comparators (e.g., DTG [n = 52], RAL [n = 167], and DRV [n = 254]) may have contributed to this association. Importantly, the Panel recommends that women who become pregnant on suppressive, EFV-containing regimens **should continue** using these regimens, as is recommended for most regimens⁷⁰ (see [Table 4](#) and [Table 5](#)).

Rilpivirine may be used as part of an *Alternative* regimen for nonpregnant adults with pretreatment HIV RNA <100,000 copies/mL and CD4 T lymphocyte (CD4) cell counts >200 cells/mm³. There are sufficient data from use in pregnancy to recommend RPV as an *Alternative* agent for ARV-naïve pregnant women who meet these same CD4 count and viral load criteria.⁷¹ Although PK data indicate that RPV plasma concentration is reduced during the second and third trimesters, the reduction is less than the reductions seen with EVG/c or DRV/c, and most women will have adequate exposure; however, viral breakthroughs have been observed. Higher-than-standard doses of RPV have not been studied, so there are insufficient data to recommend a dosing change in pregnancy. With standard dosing of RPV, viral loads should be monitored frequently (e.g., every 1–2 months; see [Monitoring of the Woman and Fetus During Pregnancy](#)).

Nevirapine is not recommended for initial ART in ARV-naïve pregnant women or for nonpregnant adults because of a greater potential for adverse effects, complex lead-in dosing, and a low barrier to resistance. **Etravirine is not recommended** for ARV-naïve pregnant patients because it is not recommended for ARV-naïve nonpregnant patients, and because there are insufficient safety and PK data on the use of ETR during pregnancy. Available PK data in women who received ETR as part of clinical care suggest that a standard adult dose is appropriate during pregnancy; unlike other ARV drugs, ETR exposure is increased during pregnancy.^{22,72} However, it may be appropriate to initiate either of these ARV drugs in special circumstances, or it may be appropriate to continue using them in ART-experienced women who become pregnant on well-tolerated, fully suppressive regimens that include these drugs.

Doravirine has not yet been studied in pregnancy; there are insufficient data to recommend its use in pregnancy.

For all women, screening for both antenatal and postpartum depression is recommended; because the use of EFV may increase the risk of depression and suicidality, this screening is particularly critical for women on EFV-containing regimens.^{67,73}

Entry and Fusion Inhibitors

Enfuvirtide and maraviroc (MVC) are not recommended for initial ART in pregnancy because they are not recommended for initial ART in nonpregnant adults, and because the safety and PK data for these drugs in pregnancy is limited. Available PK data in women who received MVC as part of clinical care suggest that a standard adult dose is appropriate during pregnancy, despite a decrease in MVC exposure during pregnancy (see [Maraviroc](#)).⁷⁴ Use of these agents can be considered for women who have experienced virologic failure with several other classes of ARV drugs and for women who become pregnant on well-tolerated, suppressive regimens that include these drugs; however, because there are insufficient data to inform safety or dosing guidance for their use in pregnancy, these drugs should only be used after consulting HIV and obstetric specialists.

Ibalizumab is a humanized monoclonal antibody to the CD4 receptor. There are no data on the use of this drug in pregnancy.

Pharmacologic Boosters

Low-dose **ritonavir** as a pharmacologic booster for other PIs, as described above, is currently the preferred pharmacologic booster for use in pregnancy. **Cobicistat**-boosted ARV drugs (ATV, DRV, or EVG) are not recommended for use in pregnancy. As noted above, EVG, **DRV, ATV**, and COBI levels have been found to be significantly lower during the third trimester than during the postpartum period.^{44,53,75} However, the Panel recognizes that there may be situations where it is appropriate to continue using these drugs in women who become pregnant on a well-tolerated, fully suppressive regimen. See [Pregnant Women Living with HIV Who Are Currently Receiving Antiretroviral Therapy](#) and [Monitoring of the Woman and Fetus During Pregnancy](#) for issues to address with patients when making decisions about whether to switch to another ARV regimen or continue the current regimen with frequent viral load monitoring.

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